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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Richard F. Trecartin
DORSEY & WHITNEY LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,307	DAHIYAT ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-6 are pending in the application and under examination.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification discloses that the present invention is directed to methods of using computational screening of protein sequence libraries to select smaller libraries of protein sequence that can be used in a number of ways. For example, the proteins can be actually synthesized and experimentally tested

in the desired assay, for improved function and properties. Similarly, the library can be additionally computationally manipulated to create a new library which then itself can be experimentally tested. However, creating a library for further screening or testing is not a substantial and a specific utility. Given its broadest interpretation, a compound library, which is collection of a million compounds, would generally have a utility. However, the law is clear in its requirement that the utility of a compound (library, as claimed) should e specific to be useful for its intended purpose. Since library is nothing more than a collection of compounds hence, it is not clear as to which compound combinations contained therein result in a utility that is substantial and specific. Nor the type of assay method applicable to the millions of resulting complex structures. The complex nature of said secondary structure, even for a known single compound, is known at times to defy such determination. The law clearly states that a patent is granted for a new and useful product, a "real world" use beneficial to the public, not prophetic or expedient statements. Nor one requiring further exploratory studies.

The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an

> invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion. Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. (emphasis added).

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the enzymes protein design using specific program design, does not reasonably provide enablement for any type of secondary library of scaffold protein variants or sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enabling disclosure is not commensurate with the scope provided in the specification. The specification, specifically the Examples discloses a method for generating secondary sequences of specific enzymes utilizing PDA. The rest of the specification discloses nothing more than general description of the claimed method. It is not readily apparent from the disclosure how other protein of secondary structure can be generated from the single example in the specification. While the enabling disclosure is not limited to the working example however, in an unpredictable art such as protein, one cannot predict the outcome of a specific protein secondary structure to a vast secondary structure or even to a single different protein. As a skilled in the art appreciates, to date there are too numerous obstacles for the design of even a single

secondary structure of a protein, let alone, all or any kinds of proteins. For example, the combinatorial large number of possible sequences and the incomplete understanding of the factors that control protein structure are still the primary obstacles in protein design. Factors such as helix propensity are important for surface design. Increasing propensity may or may not confer stability on a structure. Changes in the tertiary structure of the protein can occur. Although helix propensity appears to be more important than hydrogen bonding in stabilizing the designed coiled coils, hydrogen bonding could be important in the designing and stabilizing of other types of secondary structure. Applicants in the specification Examples recognize these limitations. Amino acid residues are selected such that cys is not used to prevent disulfide formation or Gly that can compromise flexibility and Pro for which an appropriate rotamer is difficult to define. Note further the restriction in the computer design using known primary structure of the known enzyme as obtained from the Protein Data Bank wherein water and SO2 have been deleted to remove any obstacles for its successful design. Therefore, the broad claimed method drawn to any type of library of secondary protein sequences requires an undue amount of experimentation. While computer protein design holds no barrier or limit, but ultimately the question that needs to be

asked, is if such design is feasible in the actual environment where the protein exists. The broad claimed method steps containing too numerous unknown variables are nothing more than an invitation to experiment.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps by which the mere use of a force field calculation produces a probability distribution table of amino acid residues in a plurality of variant positions and the combining of the probability distribution of amino acids results in a secondary sequence. It is not clear whether the plurality of variant positions of the

residue is relative to a peptide sequence and if so, how the table of amino acid residues is distributed along the peptide sequence by the mere use of force field calculation. Thus, there seems to be no nexus between the two steps as some steps there between are missing. It is not clear how the distribution of amino acid residues in a table is effected to be a probability residue. The term "probability' fails to ascertain the claimed invention with precision, it connotes uncertainty rendering the claim indefinite. The preamble recites for "generating a secondary library of scaffold protein sequences" while the body of the claim, recites for "a secondary library of secondary sequences". It is not clear whether the scaffold protein sequences in the preamble are the same as the secondary sequences in the body of the claims. The use of inconsistent terminologies provide for confusion and ambiguity.

B). Claim 2 is indefinite as to the steps of synthesizing a secondary sequences, if this is the scaffold, given no sequences.

C). Claim 3 is indefinite as to the oligonucleotide synthesis. The base claim recites proteins and amino acid. It is unclear as to the conversion of the peptide to the oligonucleotide.

D). Claim 5 is unclear as to the amount that "correspond" to the frequency of the mutation, given no basis as to occurrence of said frequency of mutations.

E). Claim 6 is indefinite as to the basis of "relative amounts" by which the pooled oligonucleotide is pooled.

Double Patenting

Claims 1-6 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No. 09/782,004('004). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method, which recites the force field calculation, is obviously the calculation used in the copending '004 application since a secondary structure library is similarly obtained. The instant method will be encompassed by

the '004 application which creates a primary library as a first step.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,403,312. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons set forth, supra under the provisional obviousness double patenting rejection.

[It appears that overlapping claims are being claimed in the different applications. It is requested that applicants set a demarcation line among the numerous copending applications].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayo (WO 98/47089) in view of applicants' disclosure of known prior art.

Mayo discloses e.g., page 15, lines 4-7; page 46,line 34 up to page 47, line 10 a method of creating a secondary sequence library with the side chains described as rotamers using force field calculation in generating a secondary structure for protein variants (rotamers). The conformationally site (rotamers) was varied that results in a protein having a secondary sequences different from the primary sequence from which the secondary sequences (containing a library of rotamers) are obtained. Mayo teaches the probability distribution as claimed when set of rotamers is used to replace variable positions in the template backbone (primary sequences as claimed) sequences.

Mayo does not disclose the synthesis of the protein or the nucleotides that would perhaps encode the protein (as best as the claimed can be interpreted). However, applicants admit at page 40, line 21 and lines 25-35 that "…[DNA] shuffling, as is generally known in the art, can be done with multiple libraries…….[error-prone PCR], for example using modified

nucleotides; known mutagenesis technique." Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was known to synthesize the modified sequences of Mayo using PCR methodology since this DNA method of synthesis is well known in the art of oligo synthesis as admitted by applicants in the disclosure. One having ordinary skill in the art would be motivated to sequence the optimized sequences obtained by Mayo in order to correctly identified the sequences that are contained in the library. This optimized compounds may lead to an improved compound useful for its intended purpose.

[The Mayo reference is in PTO 1449 of the copending application 09/927,790].

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0811. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
March 22, 2004